IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Hamud, Fozia M.
Kevin P. BAKER, et al.	)	Art Unit: 1647
Application Serial No. 10/006,063	)	Confirmation No: 8559
Filed: December 6, 2001	)	Attorney's Docket No. 39780-2830 P1C3
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 35489**

FILED VIA EFS
December 3, 2007

RESPONSE TO OFFICE ACTION

MAIL STOP Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the Office Action mailed on June 1, 2007, in connection with the above-identified patent application (Paper No./Mail Date 20070503), please consider the following arguments. As December 1, 2007 was a Saturday, this response is timely filed by the next business day December 3, 2007 with a request for a **three month extension of time** with necessary fees.

Also enclosed herewith is a copy of the Decision by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469).

AMENDMENTS TO THE SPECIFICATION

The title of the application has been amended as follows:

~~SECRETED AND TRANSMEMBRANE~~ PRO1293 POLYPEPTIDES ~~AND NUCLEIC ACIDS ENCODING THE SAME~~

REMARKS/ARGUMENTS

Claims 28-36 and 38-40 are pending in this application.

I. Claim Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112, First Paragraph

Claims 28-36 and 38-40 stand rejected under 35 U.S.C. §101 as allegedly lacking either a specific and substantial asserted utility or a well-established utility. (Page 4 of the instant Office Action). Claims 28-36 and 38-40 further stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement "since the claimed invention is not supported by either a credible, specific and substantial utility or a well established utility ... one skilled in the art clearly would not know how to use the claimed invention." (Page 32 of the instant Office Action).

Applicants submit, as discussed below, that not only has the PTO not established a *prima facie* case for lack of utility, but that the polypeptides of Claims 28-36 and 38-40 possess a specific and substantial asserted utility, and that based upon this utility, one of skill in the art would know how to use the claimed polypeptides without any further experimentation.

The gene amplification data disclosed in Example 143 establishes a credible, substantial and specific patentable utility for the PRO1293 polypeptides

First of all, Applicants respectfully maintain the position that the specification discloses at least one credible, substantial and specific asserted utility for the claimed PRO1293 polypeptides for the reasons previously set forth in Applicants' Responses filed on September 9, 2004 and January 28, 2005, in the Appeal Brief filed November 22, 2005 and the preliminary amendment filed on March 9, 2007.

As discussed previously, Applicants rely on the gene amplification data for patentable utility of the PRO1293 polypeptide, and the gene amplification data for the gene encoding the PRO1293 polypeptide is clearly disclosed in the instant specification under Example 143. As previously discussed, a ΔCt value of at least 1.0 was observed for PRO1293 in at least three of the tumors listed in Table 8. PRO1293 showed approximately 1.71 ΔCt units which corresponds to $2^{1.71}$- fold amplification or 3.27-fold amplification in primary lung tumor (HF-000840), and approximately 1.13-2.33 ΔCt units which corresponds to $2^{1.13}$ -$2^{2.33}$- fold amplification or 2.19 fold to 5.03-fold amplification in colon tumors (HF-000539 and HF-000795). (See Table 8 and page 507, lines 5-12 of the specification).

As further support for their utility claim, Applicants have submitted a Declaration by Dr. Audrey Goddard (made of record in the Response submitted September 9, 2004), which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. According to the Goddard Declaration, the 2.19 fold to 5.03-fold amplification of the PRO1293 gene in lung and colon tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed therein.

Applicants have also submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the corresponding mRNA and encoded protein will be expressed at an elevated level. For instance, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in the Response submitted September 9, 2004) collectively teach that in general, gene amplification increases mRNA expression. Further, Applicants have submitted over a hundred references, along with Declarations of Dr. Paul Polakis (made of record in the Preliminary Amendment of March 9, 2007 and Response of September 9, 2004), which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, as exemplified by the teachings of Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, the two Polakis Declarations, the art in general overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1293 gene, that the PRO1293 polypeptide is concomitantly overexpressed and has utility in the diagnosis of lung and colon cancer.

The Examiner maintains that the gene amplification data does not suffice to demonstrate patentable utility for the claimed PRO1293 polypeptide, because Applicants have not provided

any testing of PRO1293 mRNA or PRO1293 polypeptide expression. (Page 9 of the instant Office Action). The Examiner asserts that "Applicants merely propose a utility that is 'not implausible,' relying on a general correlation between gene amplification polypeptide expression rather than provide evidence of PRO1293 polypeptide expression." The Examiner further asserts that "[w]ithout any evidence to PRO1293 polypeptide expression this reliance on general correlations is of no avail to applicants because applicants have not established if the disclosed amplification of the PRO1293 gene is one of those cases wherein the PRO1293 polypeptide is overexpressed." From this, the Examiner concludes "the specification does not provide some immediate benefit to the public" and "merely invites the skilled artisan to determine if, or how, PRO1293 polypeptide expression changes." (Page 9 of the instant Office Action).

Applicants rely on the utility legal standard set forth in their previous office actions.

In this regard, Applicants note that under the Utility Guidelines, "a 'substantial utility' defines a 'real world' use." M.P.E.P. §2107.01, Part 1. The MPEP states for example, "[a]n assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use..." *Id.* The M.P.E.P. cautions, that "Office personnel must be careful not to interpret the phrase 'immediate benefit to the public' or similar formulations in other cases to mean that products or services based on the claimed invention must be 'currently available' to the public in order...Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[1] (Emphasis added).

To properly reject a claimed invention under 35 U.S.C. §101, the Examiner bears the initial burden of establishing a *prima facie* case that the claimed invention lacks a specific, substantial and credible utility. See M.P.E.P. §2107.02 Part IV. "where the asserted utility is not specific or substantial, a *prima facie* showing must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial." *Id.* (Emphasis added).

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[1] M.P.E.P. §2107.01.

The data presented in the specification provides the basis for at least one specific, substantial and credible utility for the claimed invention. The instant application encompasses an isolated polypeptide of SEQ ID NO:77 and sequence variants thereof. The present specification also refers to the claimed polypeptide as PRO1293. The specification discloses the data obtained using gene amplification analysis "...shows that [certain PRO polypeptide]-encoding genes are amplified in the genome of certain human lung and colon cancers and/or cell lines" and that "[a]mplification is associated with overexpression of the gene product..." (See instant specification page 494, 1st paragraph of Example 143). In particular, Table 8 explicitly indicates that the PRO1293 gene is significantly amplified in lung and colon tumors as compared to the normal control. (See page 502-503 of the instant specification). The specification expressly asserts a diagnostic utility for PRO1293 stating that "the polypeptides are useful targets for therapeutic intervention in certain cancers ...and diagnostic determination of the presence of those cancers." (See page 494, 1st paragraph of Example 143).

The asserted utility is specific, because it is specific to the diagnosis of particular conditions: lung and colon tumors. The asserted utility is also substantial because the diagnosis of lung and colon tumors constitutes a "reasonable use... that can be viewed as providing a public benefit." The asserted utility is also credible, because one skilled in the art would consider the utility to be consistent with the results of the gene amplification analyses. Thus, Applicants have provided at least one specific, substantial and credible utility.

Applicants respectfully submit that the PTO has applied an incorrect legal standard in the instant utility rejection. As explained in the Appeal Brief filed on July 27, 2005, the case law has also clearly established that Applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[2] The PTO has the initial burden to prove that Applicants' claims of usefulness are not believable on their face.[3] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility

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[2] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[3] *Ibid.*

requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[4], [5]

Applicants have previously explained that the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[6] Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant. The issue will then be decided on the totality of evidence.

A *prima facie* case of lack of utility has not been established

The Examiner alleges that the prior art does not support the correlation between gene amplification, mRNA and protein. The Examiner alleges that according to Meric et al., "[g]ene expression is admittedly, quite complicated." (Page 7 of the instant Office Action). The Examiner specifically asserts "Pennica suffices to show that DNA amplification is ***not always*** *associated with overexpression of the gene product." (Page 7 of the instant Office Action). The examiner further asserts that "the mere fact that there are opposing evidences in the art ... is a strong indication that the correlation between mRNA and protein levels is unpredictable." (Page 24 of the instant Office Action).*

Applicants submit that it is not a legal requirement to establish that gene amplification "necessarily" or "always" results in increased expression at the mRNA and polypeptide levels, or that protein levels can be "accurately predicted." As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome

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[4] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[5] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[6] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

The Examiner asserts that "[a]pplicants have never been required to establish an absolute correlation between the gene amplification with changes of mRNA and protein levels for meeting the utility standard." (Page 24 of the instant Office Action).

Yet this is precisely what the Examiner is requesting when she repeatedly states that "DNA amplification is **not always** associated with overexpression of the gene product" (Pages 7, 11 and 27 of the instant Office Action), "polypeptide levels cannot be always predicted from mRNA levels" (Page 14 of the instant Office Action) and "there are examples of genes for which such a correlation does not exist." (Page 29 of the instant Office Action). Applicants respectfully maintain that the art collectively teaches that in general, gene amplification increases mRNA expression. and the PTO has applied an incorrect legal standard in the instant utility rejection. As explained in the Appeal Brief filed July 27, 2005, the case law has also clearly established that Applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[7] The PTO has the initial burden to prove that applicants' claims of usefulness are not believable on their face.[8] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[9], [10]

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[7] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[8] *Ibid.*

[9] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[10] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

Hanna and Mornin

The Examiner cites Hanna and Mornin as showing "that gene amplification does not reliably correlate with polypeptide over-expression and thus the level of polypeptide expression must be tested empirically." (Page 6 of the instant Office Action).

Applicants respectfully point out that the Examiner appears to have misread Hanna *et al.* Hanna *et al.* clearly state that gene amplification (as measured by FISH) and polypeptide expression (as measured by immunohistochemistry, IHC) are well correlated ("in general, FISH and IHC results correlate well" (Hanna *et al.* p. 1, col. 2)). It is only a subset of tumors which show discordant results. Thus Hanna *et al.* support Applicants' position that it is more likely than not that gene amplification correlates with increased polypeptide expression.

Applicants have clearly shown that the gene encoding the PRO1293 polypeptide is amplified in a number lung and colon tumors and cell lines. Therefore, the PRO1293 gene, similar to the HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1293 gene, that the PRO1293 polypeptide is concomitantly overexpressed.

Pennica *et al.* and Konopka *et al.*

*The Examiner asserts that "Pennica and Konopka suffice to show that DNA amplification is **not always** associated with overexpression of the gene product." (Page 11 of the instant Office Action).*

Applicants' arguments presented in the previously filed Preliminary Amendment of March 9, 2007 and previous responses of record are hereby incorporated by reference in their entirety. Applicants submit that nowhere in either the Pennica or Konopka papers do the authors suggest that it is more likely than not that altered mRNA levels does not correlate with altered protein levels. On the contrary, there is a statement in Pennica that says "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression...*" (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added), which implies that the mRNA/protein correlation does exist, even if

not always, but "always" is not required by the utility standard. While Konopka show that increased mRNA and protein expression levels can result from causes other than gene amplification, when gene amplification was observed the result was an increase in mRNA and protein expression levels.

Hu *et al.*

The Examiner disagrees with Applicants' criticism on Hu et al., allegedly because the asserted utility for the claimed polypeptide is based on the presumption that increased mRNA production leads to increased protein production, and therefore, Hu et al. is directly on point by showing that the presumption is incorrect when designating proteins as diagnostic markers for cancer. (Page 12 of the instant Office Action). Regarding Applicants' criticism of Hu et al.'s statistical analysis, the Examiner asserts that Applicants are holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc. (Page 13 of the instant Office Action).

Applicants respectfully disagree and submit that Hu *et al* has not analyzed any real biological data. Hu *et al.* has only used different statistical methods to assess the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation. (See page 411, left column). Basically, Hu *et al.* has solely based their conclusions on a statistical analysis of citation frequency of a disease gene. In contrast, the association between the PRO1293 and tumor is based on solid experimental results disclosed in Example 143 (Table 8). Therefore, contrary to the Examiner's allegation, the conclusion in Hu *et al.* is based on much weaker grounds than the presently asserted utility. In addition, as Hu *et al.* has based his conclusions solely on a statistical analysis of citation frequency of a disease gene, any flaws in statistical analysis will undermine the accuracy of Hu's conclusion much more significantly than a conclusion derived from real experimental data as in the instant case.

Hu *et al.* showed only that not all genes which are found by microarray analysis to be overexpressed in breast tumors are also described in the literature as having a biological role in breast cancer. This observation may be explained by a number of reasons, including that the genes have not yet been described in the literature as having a known role in cancer; rather than the assumption put forth by the Examiner, that the genes do not have a role in cancer. Hu *et al.* did not test whether genes which are found by microarray analysis to be overexpressed in breast

tumors can be used as diagnostic markers for the tumors in which they are expressed. Thus, the Examiner has provided no reason why the various thresholds determined by Hu *et al.* for indicating whether a gene plays a biological role in one specific type of breast cancer are relevant to determining whether a gene is useful as a diagnostic marker for prostate cancer.

Regarding Applicants' criticism that Hu's teaching is limited to a specific type of breast cancer, the Examiner alleges that Hu is cited as one of several pieces of evidence that overproduction of mRNA does not correlate to protein overproduction. (Page 13 of the instant Office Action).

Applicants disagree and submit that, as discussed below, none of the cited references show a lack of general mRNA/protein correlation. Therefore, Hu, neither alone nor in combination with other cited references, teaches that overproduction of mRNA does not correlate to protein overproduction.

The Examiner alleges that, despite Applicants' criticism of Hu, the instant specification does not disclose that PRO1293 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples, therefore based on the teaching of Hu, the skilled artisan would not reasonably expect that PRO1293 protein can be used as a cancer diagnostic. (Pages 12-13 of the instant Office Action).

Applicants submit that, Hu *et al.* does not speak to the question of whether genes which are found to be amplfied in breast tumors can be used as diagnostic markers for the tumors in which they are expressed or whether gene amplification correlates with mRNA and protein overexpression. Thus, the Examiner has provided no reason why the various thresholds (such as 5 fold, 10 fold threshold) determined by Hu *et al.* for indicating whether a gene plays a biological role in one specific type of breast cancer are relevant to determining whether a gene is useful as a diagnostic marker for all types of breast cancer, let alone lung and colon cancers.

Chen *et al.* and Beer *et al.*

*The Examiner cites Chen et al. as "providing evidence that polypeptide levels cannot be **always** predicted from mRNA levels.". (Page 14 of the instant Office Action). The Examiner has further asserted that the data in Chen et al. does not meet the **more likely than not** standard because this reference discloses that only 13.7% correlation between the mRNA expression and protein level. (Pages 14-15 of the instant Office Action).*

Applicants have already addressed this issue in the previously submitted Preliminary Amendment. Applicants repeat that a review of the correlation coefficient data presented in the Chen *et al.* paper indicates that it is more likely than not that increased mRNA expression correlates with increased protein expression. A review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not." Similarly, in Table II, 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, at least 22 genes had one isoform showing a positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a significant positive correlation [as determined by the authors] for at least one isoform. No genes showed a significant negative correlation. It is not surprising that not all isoforms for each gene positively correlate with mRNA expression. As the PTO may be aware, some isoforms are likely non-functional proteins. Thus, Table II further supports Applicants' assertion that it is more likely than not that protein levels correlate with mRNA expression levels. Again, the Examiner is reminded that it is not a legal requirement to establish that gene amplification "necessarily" or "always" results in increased expression at the mRNA and polypeptide levels.

The Examiner alleges that the Chen et al. reference was published in a peer reviewed well respected journal, therefore, the data disclosed therein is taken as being correct. Further, that proper sample preparation is crucial for the 2D gel procedure, and there is no reason to assume that the Chen et al. authors did not follow proper sample preparation. (Page 16 of the instant Office Action).

Applicants disagree with the Examiner and submit that conclusions presented in a peer reviewed article are often inaccurate and sometime even erroneous due to various reasons such as poor experimental designs improper controls, flaws in data analyses, and limitations in experimental methods. As a matter of fact, authors of peer reviewed articles themselves frequently discuss the limitations of the presented data and hypotheses in the discussion section of a paper in order for the peer scientists to view the presented data more accurately. Subsequently, being presented in a peer reviewed article does not ensure a statement is accurate

at all. In this case, as discussed above, the data of Chen *et al.* has numerous flaws and should not be relied upon to make any rejections by the Examiner.

With respect Applicants' argument on Beer, the Examiner alleges that the specification of the instant application does not disclose any special feature, stage, or prognosis of lung tumor that amplify the PRO1293 gene compared to lung tumor that does not amplify the PRO1293 gene. (Page 16 of the instant Office Action).

Applicants fail to see why the present specification must disclose the same amount and same type of information as in Beer *et al.* Beer *et al.* was cited to show the existence of a correlation between increased mRNA levels in tumors and increased protein levels. As Beer *et al.* has already established the existence of a general correlation between increased mRNA levels in tumors and increased protein levels, Applicants do not need to disclose the same kind or amount of data as in Beer *et al.* to further prove Beer *et al.'s* conclusion. Instead, Applicants can simply rely on the conclusion of Beer *et al.* In addition, Applicants emphasize that neither the case law nor the Utility Guidelines requires that Applicants must disclose the same amount of experimental data in a patent application for the purpose of establishing a patentable utility as in an article published in a peer-reviewed journal, where extensive experimental details are typically provided. On the contrary, the Office personnel must treat as true a statement of fact made by an Applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. One of ordinary skill in the art would not have a legitimate basis to doubt the credibility of the results of the present application because Beer *et al.* has established the correlation between increased mRNA levels in tumors and increased protein levels.

Haynes *et al.*, Gygi *et al.* and Futcher *et al.*

The Examiner maintains that the Haynes et al. reference establishes that "protein expression levels are not predictable from the mRNA expression levels...and only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts." (Page 18 of the instant Office Action).

As a preliminary matter, it is not a legal requirement to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be

accurately predicted. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Indeed, contrary to the Examiner's reading, Haynes teaches that "there was a *general trend but no strong correlation* between protein [expression] and transcript levels." (Emphasis added). For example, in Figure 1, there is a positive correlation between mRNA and protein levels amongst most of the 80 yeast proteins studied. In fact, very few data points deviated or scattered away from the expected normal and no data points showed a negative correlation between mRNA and protein levels (*i.e.,* an increase in mRNA resulted in a decrease in protein levels). The analysis by Haynes *et al.* is not relevant to the current application. Haynes was studying yeast cells and not human cells. Haynes *et al* notes that their analysis focused on the 80 most abundant proteins in the yeast lysate. (Page 1867). Haynes *et al.* states "since many important regulatory protein are present only at low abundance, these would not be amenable to analysis." (Page 1867). Further, Haynes *et al.* compared the protein expression levels of these naturally abundant proteins to mRNA expression levels from published SAGE frequency tables. (Page 1863). Accordingly, Haynes *et al.* did not compare mRNA expression levels and protein levels in the same yeast cells. Thus, the analysis by Haynes *et al.* is not applicable to the present application.

The PTO also maintains the assertion that Gygi et al. "teaches that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data" (Page 18 of the instant Office Action).

Applicants have also already analyzed the teaching of Gygi *et al.* and submitted that this reference shows general correlation between mRNA and protein. Applicants maintain the same position.

Applicants submit that Gygi *et al.* clearly teach that "there was a general trend of increased protein levels resulting from increased mRNA levels." (Emphasis added. See

page 1726, left column, second paragraph and Figure 5). In response to the Examiner's assertion that Gygi *et al.* teach that the correlation between mRNA and protein levels was insufficient to **predict** protein expression levels from quantitative mRNA data, Applicants maintain the law does not require the existence of a "necessary" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately predicted." According to Gygi, the data confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and show that a positive correlation exists between mRNA and protein.

With respect to Futcher et al., who did study a extensive number of genes across the entire yeast genome, the Examiner asserts that Futcher's conclusions apply only to relatively abundant proteins, and that Futcher "also admits that Gygi et al. performed a similar study and generated similar data, but reached a different conclusion." (Pages 19-20 of the instant Office Action).

It appears that the Examiner reaches the same conclusion as Applicants, that is, the data in Futcher validates the use of mRNA abundance as a rough predictor of protein abundance. The Examiner seems to invalidate the conclusion of Futcher by pointing out that Gygi reaches a different conclusion. Applicants have already analyzed the teaching of Gygi and submit that Gygi teaches that a general correlation between mRNA and protein exists. In addition, as Futcher is published later than Gygi, Futcher's conclusion should be considered as the updated view in the art.

As discussed previously in the Preliminary Amendment of March 9, 2007 in the section concerning Gygi *et al.*, Futcher et al. convincingly demonstrated that the different conclusions of Gygi *et al.* were due to deficiencies in the data analysis and collection techniques used by Gygi *et al.*

The Examiner asserts that "[t]here is no guidance in the specification as to how high the levels of overexpression are. If a clinician took a colon or breast tissue sample from a patient with suspected colon or breast cancer, what is the likelihood that when compared with normal tissue, the level of PRO1293 from the patient would be higher? How many samples would be needed? What sensitivity would be needed? ..." etc. (Page 20 of the instant Office Action).

These remarks are a clear indication that the Examiner applies a standard that might be appropriate if the issue at hand were the regulatory approval of a diagnostic assay based on the overexpression of PRO1293 in lung and colon tumors, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA, reviewing an application for a new diagnostic assay, will indeed ask for actual numerical data, statistical analysis, and other specific information before a diagnostic assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards of market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States.[11] Indeed, in *Nelson v. Bowler*,[12] the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to a diagnostic utility as well. The identification of a diagnostic utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

The Examiner further notes that she was unable to locate a citation in Futcher et al indicating that the Gygi data confirm that there is a general trend between protein expression and transcript levels, as asserted by Applicants. By contrast, the Examiner points out that Futcher state, "Gygi et al feel that mRNA abundance is a poor predictor of protein abundance and that codon bias is not a predictor of either protein or mRNA levels." (Page 20 of the instant Office Action).

Applicants reiterate that Gygi *et al.* clearly teach that "there was a general trend of increased protein levels resulting from increased mRNA levels." (Emphasis added. See page 1726, left column, second paragraph and Figure 5). Applicants further submit that while Gygi *et al.* state that the correlation may not be sufficient in **accurately** predicting protein level from the level of the corresponding mRNA transcript (Emphasis added) (see page 1270, Abstract), *accurate prediction* is not a criteria that is necessary for meeting the utility standards. Nevertheless, the Gygi data shows a strong correlation for the most abundant proteins, but a poor

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[11] *Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994).

[12] *Nelson v Bowler*, 626 F.2d 853, 856, 206 U.S.P.Q. 881, 883 (CCPA 1980).

correlation for the least abundant proteins in their data set. Futcher *et al.* point out that "**the poor correlation of protein to mRNA for the nonabundant proteins of Gygi *et al.* may reflect difficulty in accurately measuring these nonabundant proteins and mRNAs, rather than indicating a truly poor correlation *in vivo***" (page 7367, col. 2; emphasis added). Applicants point out to the examiner that codon bias as a predictor of either protein or mRNA levels is not relevant to the instant utility.

Lian *et al.*, Fessler *et al.* *and* Greenbaum *et al.*

The Examiner maintains that Lian, Fessler and Greenbaum show that there is a poor correlation between mRNA expression and protein abundance. In response to Applicants' arguments that Lian et al. disclose several caveats for broad classes of proteins, the Examiner asserts that "this reference was published in a peer reviewed well, respected journal, therefore, the data disclosed therein is taken as being correct." (Page 22 of the instant Office Action). The Examiner further asserts that "the fact that the total number of proteins examined by Lian et al. was only 50 as compared to the 7000 genes for which mRNA levels were measured is irrelevant." (Page 22 of the instant Office Action).

Applicants have already analyzed the teaching of these two references in the Preliminary Amendment of March 9, 2007. Applicants maintain the same position and note that both Fessler *et al.* and Lian *et al.* have relied on insensitive and inaccurate methods of measuring protein expression levels. The teachings of these two references cannot be relied upon to establish a *prima facie* showing of lack of utility. Further, as discussed above, Applicants submit that being presented in a peer reviewed article does not ensure a statement is accurate at all. In fact, conclusions presented in a peer reviewed article are often inaccurate and sometime even erroneous due to various reasons such as poor experimental designs improper controls, flaws in data analyses, and limitations in experimental methods. Indeed, authors of peer reviewed articles themselves frequently discuss the limitations of the presented data and hypotheses in the discussion section of a paper in order for the peer scientists to view the presented data more accurately.

Applicants respectfully submit that the fact that many more transcripts than proteins were found to be differentially expressed does not mean that most mRNA changes did not result in correlating protein changes, but merely reflects the fact that expression levels were only

measured at all for many fewer proteins than transcripts. In particular, the total number of proteins whose expression levels were examined by Lian *et al.* was only 50 (page 520, col. 2), as compared to the approximately 7000 genes for which mRNA levels were measured. (Page 515, col. 1). Lian *et al.* further point out that those proteins whose expression were measured are a far from representative set, stating that "[t]hese data must be considered with several caveats: membrane and other hydrophobic proteins and very basic proteins are not well displayed by the standard 2DE approach, and proteins presented at low level will be missed. In addition, to simplify MS analysis, we used a Coomassie dye stain rather than silver to visualize proteins, and this decreased the sensitivity of detection of minor proteins." (Page 520, col. 1; Emphasis added). Thus, it is hardly surprising that the authors did not happen to include in this very small and atypical set of proteins more of those that were products of the 837 out of 7000 genes showing differential expression at the mRNA level.

Applicants note that the Examiner also appears to have misinterpreted the findings of Fessler *et al.*, stating that the authors identified 100 upregulated genes but only 8 upregulated proteins. In fact, Fessler *et al.* identified about 100 upregulated proteins in each experiment. (Page 31293, col. 2). Applicants also note that Fessler *et al.* found far more proteins than genes to be expressed in PMNs, detecting 923 genes (page 31293, col. 1) but estimating that over 10,000 proteins were expressed in PMNs. (Page 31293, col. 2). For this reason it is not surprising that, as shown in Table VIII, most of the upregulated proteins did not have corresponding probes on the microarray chip; thus it was impossible to determine if the mRNAs corresponding to these proteins showed correlating expression changes.

In addition, as was the case with Lian *et al.*, the proteins analyzed by Fessler *et al.* are a small and unrepresentative subset of all proteins expressed in the studied cell type. As admitted by Fessler *et al.*, protein identification by two-dimensional PAGE limited to well-resolved regions of the gel, may perform less well with hydrophobic and high molecular weight proteins, and tends to select for more abundant protein species. (Page 31301, col. 1). Furthermore, "the post-LPS incubation, pre-two-dimensional PAGE cell washes **would be expected to remove secreted proteins from further analysis.**" (Page 31301, col. 1; Emphasis added). In addition, because protein binding of Coomassie Blue has a limited dynamic range and is typically not linear throughout the range of detection, image analysis of Coomassie Blue-stained protein spots

should only be consider as semi-quantitative. (See page 31301, col. 1). Thus, again, in this study, not only were low abundance proteins underrepresented, but secreted proteins were selectively removed from the analysis. As the proteins in the present application are secretory proteins, the results of Fessler's study cannot be applied to the proteins of the present application.

Applicants next note that cases in which protein levels changed while mRNA levels were unchanged are not relevant, since Applicants are not asserting that changes in mRNA levels are the only cause of changes in protein levels. Applicants further note that, as discussed in the Preliminary Amendment filed on March 9, 2007, in 5 of the 6 cases for which a change in mRNA levels are reported, the change in the level of mRNA corresponds to the change in the level of the protein. This is consistent with Applicants' assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein.

With respect to Greenbaum, Applicants have already analyzed the teaching of this reference in the Preliminary Amendment of March 9, 2007. Applicants maintain the same position and note that, contrary to the Examiner's assertion, Greenbaum does find high levels of correlation between mRNA and protein expression in yeast cells. In particular, Greenbaum demonstrates that a high degree of correlation is found for those genes which show a large degree of variability in mRNA expression – that is, for those genes which show changes in mRNA expression, the change in mRNA expression is correlated with a change in protein expression.

In summary, Applicants respectfully submit that the Examiner has not shown that gene amplification in tumor as compared to normal tissue is not correlated with changes in mRNA and protein expression. The Patent Office has failed to meet its initial burden of proof that Applicants' claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the Pennica, Konopka, Hu, Chen, Haynes, Gygi, Lian, Fessler, and Greenbaum articles do not provide sufficient reasons to doubt the statements by Applicants that PRO1293 has utility. As discussed above, the law does not require the existence of a "necessary" correlation between gene amplification and mRNA and protein expression levels. Nor does the law require that protein levels be "accurately predicted." According to the authors themselves, the data in the above cited references confirm that there is a general trend between gene amplification and mRNA and protein expression levels, which meets the "more likely than

not standard" and show that a positive correlation exists between gene amplification and mRNA and protein expression. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is overexpressed in cancer, it is more likely than not that the encoded protein will also be expressed at an elevated level.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (of record in Information Disclosure Statement filed on September 9, 2004) and the articles by Bea *et al.* and Godbout *et al.* (made of record in Preliminary Amendment of March 9, 2007) collectively teach that in general, gene amplification increases mRNA expression.

Second, Applicants have submitted over a hundred references, along with the Declarations of Dr. Paul Polakis with their Preliminary Amendment filed on March 9, 2007, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Third, Applicants would like to bring to the Examiner's attention a recent decision by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9 of the Decision). Applicants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO1293 polypeptide to refute Applicants' assertion of a correlation between mRNA levels and protein expression.

Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*

The Examiner alleges that "Orntoft et al., Hyman et al., and Pollack et al. are evidence that at the time of applicants' invention one would not know if PRO1293 gene amplification is

positively correlated with PRO1293 polypeptide expression. (Page 26 of the instant Office Action).

Applicants maintain, for the reasons previously made of record, that Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*collectively teach that in general, gene amplification increases mRNA expression. Applicants further respectfully submit that the Examiner has provided no arguments or evidence as to why the data from Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*, concerning gene expression in bladder and breast tumors, would not also apply to tumors in general.

Polakis Declaration

With respect to the Polakis II Declaration, the Examiner asserts that "[t]he fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between a change, if any, in PRO1293 transcripts and PRO1293 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist." (Page 29 of the instant Office Action).

Dr. Polakis' Declarations provide evidence, in the form of statements by an expert in the art, that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." The PRO1293 gene was found to be amplified in lung and colon tumors. As discussed above and in Applicants' previous Responses, one of ordinary skill in the art would therefore expect the PRO1293 mRNA to be overexpressed in the same human lung and colon tumor samples. Accordingly, one of ordinary skill in the art would understand that the PRO1293 polypeptide would be expected (more likely than not) to be overexpressed in human lung and colon tumor samples relative to their normal human tissue counterparts, as are the majority of other molecules tested.

As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility.

Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[13] which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Polakis Declaration) states: "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis declaration, this rejection is improper under both the case law and the Utility guidelines.

References submitted by Applicants

With respect to the 118 additional references cited by Applicants to support their position that, in general, amplification of a particular gene leads to a corresponding change in the level of expression of the mRNA and encoded protein, the Examiner asserts that "none of the cited references address the major issue in this rejection, which is whether or not the PRO1293 gene amplification in lung and colon tumor leads to overexpression of the PRO1293 polypeptide in said tumors." (Page 31 of the instant Office Action).

Applicants submit that 118 references do not need to provide any data specific for PRO1293 because the data was provided as a proof of existence of a general correlation (more likely than not) between mRNA and protein expression for any given gene. Applicants are not required either under the law or under the Utility Guideline to prove that there is "absolute certainty" that mRNA/protein correlation exists for PRO1293. Therefore, Applicants should not be required to provide any specific information for PRO1293, such as the sequences that are represented by the UNQ numbers; the objective staining intensity; the absolute magnitude of the

[13] Part IIB, 66 Fed. Reg. 1098 (2001).

mRNA and protein were overexpressed, etc.

Based on the above arguments, Applicants have clearly demonstrated a credible, specific and substantial asserted utility for the claimed PRO1293 polypeptides, for example, as diagnostic markers for lung and colon tumors. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

Applicants therefore respectfully request withdrawal of the rejections of Claims 28-36 and 38-40 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

II. Claim Rejections Under 35 U.S.C. §112, First Paragraph, Written Description

Claims 28-32 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description for the recited variant polypeptides.

Applicants respectfully maintain the position that that Claims 28-32 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in Applicants' Responses filed on September 9, 2004 and January 28, 2005, in the Appeal Brief filed November 22, 2005 and the preliminary amendment filed on March 9, 2007.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned agent at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C3**)

Respectfully submitted,

Date: December 3, 2007

By: _____
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